

IN THE DRAWINGS

A set of replacement drawings is supplied herewith, including corrected Fig. 11C.

REMARKS

Reconsideration and withdrawal of the objections to the specification, and objections and rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1-2, 4, 13, 15-16, 20, and 23 are amended, and claim 3 is canceled. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the above-referenced application. Claims 1-2 and 4-53 are now pending in this application.

Objection to Declaration

A substitute Oath/Declaration is enclosed, thereby obviating the objections thereto at page 5 of the Office Action.

Objection to Drawings

A substitute Figure 11C is enclosed herewith, along with replacement sheets for all figures, thereby obviating the objections thereto at page 5 of the Office Action.

Specification Objections

The Examiner requests that Applicant distinctly identify by page and line number with a concise explanation of the relevance any statements within a citation directly applicable to the instantly claimed invention. Applicant asks that the Examiner clarify this request, e.g., what is "a citation directly applicable to the instantly claimed invention", as Applicant has submitted Forms 1449 in compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq.*, and the Examiner has initialed and returned those Forms 1449.

At pages 4-5 of the Office Action, the Examiner objected to pages 1, 13-15, 28, 43, 70-71, 75-76, and 101 of the specification under 35 U.S.C. § 112, first paragraph. The amendments to pages 1, 28, 43, and 70 address the objections thereto.

With regard to the use of "doxorubicin" and "doxyrubicin" in the specification, those terms are synonymous.

Although it is disclosed that the bioavailability of DOXIL[®] to cell culture cells is unclear, as the active ingredient in DOXIL[®] is doxorubicin, in the context of the particular data disclosed in the specification (*in vitro* versus *in vivo*), the use of "DOX" in the specification is clear.

With respect to the identity of "RLU" in Figure 2, the Examiner is requested to consider page 78 in the specification which discloses a luciferase-based assay. The Examiner is requested to note that the results from such an assay are routinely reported as relative luminescence units (see, for instance, Brief Description of Figure 3).

The units "ng/nL" and "mU" in Table 2 relate to the amount of Factor VIII (in ng/nL or mU/mL) in animals determined using an ELISA or Coatest (known methods, see page 73, lines 29-31 in the specification, and IMUBIND[®] Elisa kit brochure and abstract for Gnatenko et al., Br. J. Hemato., 104:27 (1999) and Dinesen et al. (Thromb. Res., 31:707 (1983) (a copy of each is enclosed)).

Therefore, withdrawal of the objections to the specification under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims Objections

The Examiner also objected to claims 13, 15-16, 20 and 23 under 37 C.F.R. § 1.175(c). The amendments to claims 13, 15-16, 20, and 23 obviate the objection thereto under 37 C.F.R. § 1.175(c).

The 35 U.S.C. § 112 Rejections

Claims 1-7, 13, 15-16, 20, and 23 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. In particular, the Examiner asserts that 1) the breadth of the claims is exceptionally large, encompassing an enormous genus of undefined symptoms of an enormous genus of etiologically and pathologically distinct diseases associated with aberrant expression or activity of an epithelial sodium channel (ENaC), where the quantitative values by which an artisan would know *a priori* that the expression or activity of the enormous genus of epithelial sodium channels are "aberrant" is neither defined nor disclosed; 2) the claims are also broad for encompassing an enormous genus of distinctly different physical, chemical and cell biological processes that may be affected by an agent so as to enhance the "efficacy" of an enormous genus

of structurally and functionally distinct gene therapy vectors, where the term "efficacy" is not defined; and 3) there is no disclosure in the specification teaching the nexus between an antibiotic and the treatment of a disease caused by an aberrant expression of amiloride-sensitive epithelial sodium channel proteins and no disclosure in the specification teaching the nexus between an antibiotic and how the antibiotic alters expression or activity of amiloride-sensitive epithelial sodium channel proteins α ENaC, β ENaC and γ ENaC. This rejection is respectfully traversed.

As amended, the claims do not recite "efficacy", "disease", or "symptoms".

It is well-settled that it is not necessary that a patent applicant have prepared and tested all the embodiments of his invention in order to meet the requirements of § 112. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Furthermore, enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). In fact, a considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Thus, if Applicant's invention is disclosed so that one of ordinary skill in the art can practice the claimed invention, even if the practice of the invention by the art worker includes routine screening or some experimentation, Applicant has complied with the requirements of 35 U.S.C. § 112, first paragraph. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976); Ex parte Jackson, 217 U.S.P.Q. 804 (Bd. App. 1982).

The claims are directed to methods of screening for agents with a certain second activity.

In particular, claim 1 is directed to a method which includes selecting one or more agents which inhibit expression or activity of amiloride-sensitive ENaC having α , β and γ subunit of ENaC; contacting *in vitro* mammalian cells with the one or more agents and a viral gene therapy vector; and identifying an agent from those contacted with the mammalian cells that enhances the transduction of the viral gene therapy vector relative to mammalian cells contacted with the viral gene therapy vector but not contacted with the one or more agents. Claim 2 is directed to a method which includes selecting one or more agents that enhance the transduction of a viral gene therapy vector in mammalian cells; contacting *in vitro* mammalian cells having aberrant

expression or activity of amiloride-sensitive ENaC having α , β and γ subunits of ENaC with the one or more agents; and identifying an agent from those contacted with the mammalian cells that alters ENaC expression or activity.

The specification discloses how to test for agents that have the recited dual activities (pages 4-7, and Examples 1-2, 4-5 and 7-9), e.g., viral transduction assays are disclosed in Examples 1-2, 4-5 and 7 and ENaC assays are disclosed in Examples 8-9, discloses agents that may be useful in the methods of the invention (pages 4-6 and 27-34, Examples 1-2 and 4, and claims 4, 16-23, 28-32 and 46), and how to use agents with those activities (pages 7-12). Moreover, the specification discloses methods that provide objective, quantitative values on relative expression or activity of the α , β and γ ENaC subunits. It is Applicant's position that it is well within the skill of the art worker to compare test values to control values to determine whether the test values are substantially the same or different, e.g., "aberrant", than the control values.

As the specification clearly enables the claimed invention, withdrawal of the § 112(1) rejection is respectfully requested.

Claims 1-7, 13, 15-16, 20, and 23 were rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Specifically, the Examiner asserts that i) the term "efficacy" in the claims is a relative term which renders the claims indefinite; ii) as the art recognizes a multitude of structurally and functionally distinct gene therapy vectors, the metes and bounds of "gene therapy vectors" are indefinite; and iii) the phrase "epithelial sodium channels" is indefinite. These rejections are respectfully traversed.

The amendments to claims 1-2 address bases 2-3 of the § 112(2) rejection.

With respect to "efficacy", it is Applicant's position that that term is conventionally used and understood by the art (see page 592 in Churchill's Medical Dictionary, Churchill Livingstone Inc., 1989 (a copy is enclosed herewith). Nevertheless, to advance prosecution, the word "efficacy" no longer appears in the claims.

Therefore, withdrawal of the § 112(2) rejections is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 1-5, 7, 15-16, 20, and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yalkinoglu et al. (Int. J. Cancer, 45:1195 (1990)), Bohl et al. (Blood, 92:1512 (1998)) or Schwarzbach et al. (Int. J. Oncology, 20:1211 (2002)). These rejections are respectfully traversed.

Yalkinoglu et al. disclose infection of CHO cells with AAV-2 and, 6 hours later, a 2 hour treatment with a carcinogen (MNNG) (page 1196). 72 hours after carcinogen treatment, it is disclosed that the cells were analyzed for DNA amplification or trypsinized and seeded for selection in methotrexate (MTX)- or adriamycin (ADR)-containing media (page 1196). It is also disclosed that infection of cells with AAV-2 prior to treatment with MNNG markedly inhibited carcinogen-induced drug resistance, while infection of AAV alone did not exert any effect (abstract). There is no mention in Yalkinoglu et al. that MNNG, MTX or ADR enhanced AAV transduction or altered ENaC expression or activity.

Bohl et al. disclose that intramuscular infection of mice with a rAAV that expresses erythropoietin (epo) via a doxycycline responsive promoter, and subsequent administration of doxycycline (beginning 2 weeks after infection), resulted in control of hematocrit and serum epo concentrations (abstract and page 1514). As Bohl et al. administered doxycycline 2 weeks after rAAV infection, it is unlikely that doxycycline administration altered AAV transduction.

Schwarzbach et al. disclose that the cytotoxic effect of doxorubicin treatment (for 12-24 hours) of human sarcoma cell lines was enhanced by subsequent infection with AAV-2 (abstract and page 1212). There is no mention in Schwarzbach et al. of the effect doxorubicin had on AAV transduction.

The Examiner acknowledges that the cited art does not teach that 1) an antibiotic treats one or more symptoms of a disease which is associated with aberrant expression or activity of an epithelial sodium channel, 2) mammalian cells have aberrant expression or activity of epithelial sodium channels, and 3) antibiotics modulate transcription of one or more molecules that regulate ENaC transcription.

However, the Examiner asserts that the disclosed antibiotics inherently possess the recited properties, and the disclosed cells have some degree of aberrant expression or activity of ENaC. The Examiner then concludes that it would have been obvious to one of ordinary skill in

the art to modify the methods of Yalkinoglu et al., Bohl et al. and/or Schwarzbach et al. to identify one or more agents with dual therapeutic activity with a reasonable chance of success because the cited prior art performed the recited method steps, observed phenotypic effects on the gene therapy vector and/or cells caused by the administration the selected agent, and thus have effectively identified an agent with dual therapeutic activity. The Examiner continues asserting that an artisan would be motivated to modify the methods of the cited prior art because the art did not directly ascertain the nature and degree of epithelial sodium channel expression or activity in the target mammalian cells, nor measure changes in epithelial sodium channel expression or activity as a response to the administration of the agent and viral vector to the target mammalian cells.

First, a rejection based on “inherency” is appropriate under § 102 not § 103.

Second, none of the cited art alone or in combination discloses or suggests, or provides a motivation for, a screening method to identify an agent that enhances the transduction of a viral gene therapy vector and alters ENaC expression or activity. In particular, contrary to the Examiner’s assertion that the cited prior art performed the recited method steps, none of the cited art teaches or suggests identifying an agent which enhances the transduction of a viral gene therapy vector, that also alters ENaC expression or activity, or identifying an agent which inhibits ENaC expression or activity, that also enhances the transduction of a viral gene therapy vector.

And without the recognition that agents can have the recited dual activities, i.e., in the absence of Applicant’s disclosure, there is nothing in the cited art that provides the motivation, or reasonable expectation of success, for the identification of such agents.

Therefore, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

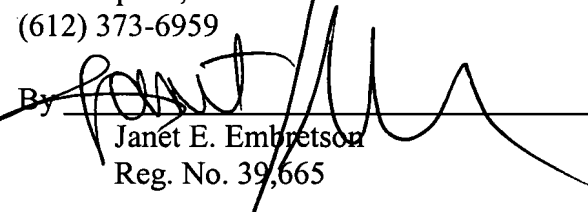
Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,


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Date August 21, 2007

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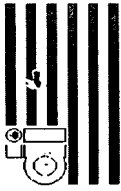
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IMUBIND® FVIII ELISA Kit

Product No. 884CON

for measuring human factor VIII
in purified concentrates

INTENDED USE

The IMUBIND® FVIII ELISA kit is an enzyme-linked immunoassay for the quantitation of human factor VIII purified concentrates originating from plasma or cell culture supernatants. The assay recognizes native and recombinant human factor VIII with equal efficiency. There is limited cross-reactivity with factor VIII from other species.

This assay is for research use only. It is not intended for diagnostic or therapeutic procedures. The assay's use with patient plasma is under investigation and remains undefined.

INTRODUCTION

Factor VIII (FVIII) is a glycoprotein essential for the intrinsic pathway of blood coagulation because of its ability to accelerate the proteolytic activation of Factor X (FX) by the serine protease Factor IXa (FIXa).¹ Synthesized mainly in hepatocytes, the mature form of FVIII is a single-chain, 2332 amino acid polypeptide, with a molecular ratio of approximately 265,000 Daltons. The molecule is comprised of two homologous groups separated by a third segment and organized with the domain structure of A1-A2-B-A3-C1-C2.² Cleaved intracellularly into a two-chain heterodimer, a heavy-chain of domains A1-A2-B and a light-chain of domains A3-C1-C2, FVIII is secreted into the blood stream and forms a stable, non-covalent complex with von Willebrand Factor (vWF)^{3,4}. FVIII is activated by proteolytic cleavage and released from its vWF carrier protein by thrombin².

The activated protein, FVIIIa, consists of the domains A1-A2 and the A3-C1-C2 light chain, both of which are necessary for sustained activity.⁵ The B domain does not contribute to the active molecule and is lost after activation.^{6,7} FVIIIa is a cofactor for FIXa along with calcium and phospholipids. Binding to phospholipids and to platelets occurs via the light chain and has been determined to be associated with sequences within the C domain.⁸ The light chain is also responsible for the binding to vWF⁹.

BIOLOGICAL SIGNIFICANCE

The role of FVIII in blood coagulation is demonstrated by the severe bleeding associated with hemophilia A, FVIII genetic deficiency. Along with hemophilia B, FIX deficiency, it occurs at a frequency of 1/10,000 of the whole population. In healthy normal individuals, FVIII is found circulating in plasma at a concentration of 100 - 200 ng/mL¹⁰.

The severity of hemophilia A is associated with the level of deficiency: mild being 5-40% of normal, moderate being 1-5% of normal, and severe being < 1% of normal. Hemophilia A is first diagnosed by clinical situation (family history) or the appearance of bleeding during the neonatal period. Severe hemophilia is usually diagnosed within the first year of life from a number of bleeding manifestations such as deep muscle and joint hemorrhaging and easy bleeding, or by post-trauma bleeding in later years. Mild

hemophilia may not be diagnosed until year 10 or later¹¹. The diagnosis is confirmed by a plasma assay for FVIII and successful treatment for moderate and severe deficiencies is accomplished by administration of FVIII concentrates.

PRINCIPLE OF THE METHOD

The IMUBIND FVIII ELISA is a "sandwich" ELISA using a monoclonal antibody against human factor VIII as the capture antibody. Samples incubate in precoated micro-test wells and a second monoclonal antibody, horseradish peroxidase (HRP) conjugated, is used to detect the bound FVIII antigen. The addition of a perborate/3,3',5,5'-tetramethylbenzidine (TMB) substrate, and its subsequent reaction with the HRP creates a blue colored solution. Sensitivity is enhanced by addition of a 0.5N sulfuric acid stop solution, yielding a yellow color. FVIII levels are determined by measuring solution absorbances at 450 nm and comparing the values to those of a standard curve generated using calibrated antigen.

REAGENTS

- 6 x 16 well precoated micro-test strips with holder and lid
- 6 vials fVIII standards, 0 - 200 mU/mL (lyophilized)
- 1 vial Detection Antibody, HRP-conjugated anti-human fVIII (135 µL)
- 2 vials Assay Diluent (lyophilized)
- 1 vial Substrate, TMB (11 mL)
- 1 packet Wash Buffer, PBS with 0.05% Tween 20, pH 7.4

ADDITIONAL MATERIALS REQUIRED BUT NOT PROVIDED

- 0.22 µm filtered deionized H₂O
- 50-200 µL eight channel multi-pipette
- 10-200 µL single pipette
- Micro-test plate reader at 450 nm
- 0.5N H₂SO₄

PREPARATION OF THE REAGENTS

A. fVIII Standards

Note: fVIII standards should be prepared just prior to use in the assay. Do not prepare standards in advance.

1. Add 1.0 mL filtered deionized H₂O to each of the **Standard** vials.
2. Agitate gently. Do not shake!

B. Assay Diluent

Add 20 mL of filtered deionized H₂O to each of the **Assay Diluent** vials and mix well.

C. Wash Buffer

1. Dissolve the contents of the **Wash Buffer** packet in 900 mL of filtered deionized H₂O.
2. Q.S. to a final volume of 1 Liter with distilled H₂O.
3. Mix well and confirm pH is 7.4 (adjust if necessary).

REAGENT STABILITY

Store unused micro-test strips and unreconstituted reagents at 2-8°C until the expiration date indicated on their labels. Aliquot and freeze reconstituted standards at -20°C. Store reconstituted reagents at 4°C for up to one month.

SAMPLE PREPARATION

Dilute fVIII concentrates at various ratios (1:100, 1:200, 1:500, etc.) with Assay Buffer until the sample produces an absorbance within the bounds of the standard curve.

ASSAY PROCEDURE

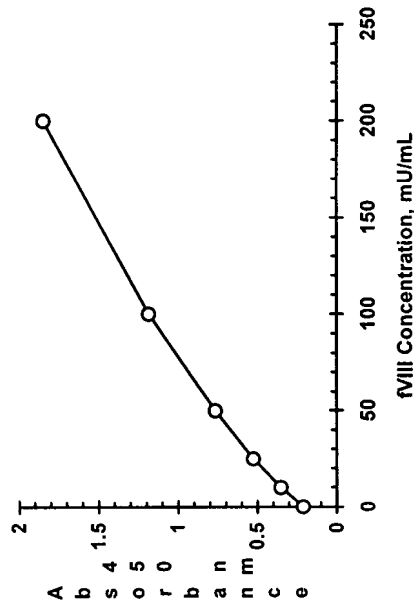
1. Remove the necessary number of precoated micro-test strips from the foil pouch and place them in the plate holder. Tightly reseal the foil pouch with the desiccant inside and store at +2°C - +8°C.
2. Add 50 µL of **fVIII Standards** or diluted sample to the micro-test wells. Perform measurements in duplicate.
3. Add 100 µL of **Assay Diluent** to each well and incubate for 90 minutes at room temperature.
4. Wash wells 4 times with **Wash Buffer** (250 µL per well).
5. For each micro-test strip used, add 20 µL of HRP-conjugated **Detection Antibody** to 2 mL of **Assay Diluent**. Add 100 µL of diluted detection antibody to each well, cover with the lid and incubate for 60 minutes at room temperature.
6. Wash wells 4 times with **Wash Buffer** (250 µL per well).

7. Add 100 μL of **Substrate** solution to each well, cover with lid and incubate for 20 minutes at room temperature. A blue color will develop.
8. Stop the enzymatic reaction by adding 50 μL of 0.5N H_2SO_4 . Tap the sides of the strip-wells to ensure even distribution of the H_2SO_4 . The solution color will turn yellow. Read the absorbance of the solutions on a micro-test plate reader at a wavelength of 450 nm immediately. The background average of the "0" standard may be deducted from the absorbance of the remaining standards and the sample readings.

REPRESENTATIVE STANDARD CURVE

The standard curve is constructed by plotting the mean absorbance value calculated for each FVIII standard versus its corresponding concentration. A standard curve should be generated each time the assay is performed.

IMUBIND® FVIII ELISA



CALCULATION OF RESULTS

Use the mean absorbance value for each diluted sample to interpolate its FVIII concentration from the standard curve. Multiply the concentration determined from the standard curve by the dilution factor to obtain the FVIII concentration in the original sample.

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Human factor VIII can be packaged and functionally expressed in an adeno-associated virus background: applicability to haemophilia A gene therapy



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Abstract:

Adeno-associated virus (AAV) is a single-stranded DNA parvovirus displaying several attractive features applicable to haemophilia A gene therapy, including non-pathogenicity and potential for long-term transgene expression from either integrated or episomal forms. We have generated and characterized two B-domain-deleted (BDD) fVIII mutants, deleted in residues Phe⁷⁵⁶ to Ile¹⁶⁷⁹ (fVIIIΔ756-1679) or Thr⁷⁶¹ to Asn¹⁶³⁹ (fVIIIΔ761-1639). [³⁵S]metabolic labelling experiments and immunoprecipitation demonstrated intact BDD-fVIII of the predicted size in both lysates and supernatants ($M_r \sim 155$ kD for fVIIIΔ756-1679 and $M_r \sim 160$ kD for fVIIIΔ761-1639) after transient transfection into COS-1 cells. Functional fVIII quantification appeared maximal using fVIIIΔ761-1639, as evaluated by Coatest and clotting assay (98 ± 20 mU/ml/ 1×10^6 cells and 118 ± 29 mU/ml/ 1×10^6 respectively, collection period 48 h). To bypass potential size limitations of rAAV/fVIII vectors, we expressed fVIIIΔ761-1639 using a minimal human 243 bp cellular small nuclear RNA (pHU1-1) promoter, and demonstrated fVIII activity $\sim 30\%$ of that seen using CMV promoter. This BDD-fVIII (rAAV(pHU1-1) fVIIIΔ761-1639) can be efficiently encapsidated into rAAV (107% of wild type), as demonstrated by replication centre and DNAase sensitivity assays. A concentrated recombinant viral stock resulted in readily detectable factor VIII expression in COS-1 cells using a maximally-achievable MOI ~ 35 (Coatest 15 mU/ml; clotting assay 25 ± 2.0 mU/ml/ 1×10^6 cells). These data provide the first evidence that rAAV is an adaptable virus for fVIII delivery, and given the recent progress using this virus for factor IX delivery *in vivo*, provide a new approach towards definitive treatment of haemophilia A.

Keywords: factor VIII; genetics; haemostasis; thrombosis;

coagulation

Document Type: Research article

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1: [Thromb Res. 1983 Sep 1;31\(5\):707-18.](#)

Links

An enzyme immunoassay (ELISA) for the quantitation of human factor VIII coagulant antigen (VIII:CAG).

Dinesen B, Feddersen C.

For the purposes of prenatal diagnosis and carrier detection of haemophilia A, an enzyme linked immunosorbent assay (ELISA) was developed for the quantitation of plasma Factor VIII coagulant antigen (VIII:CAG). It is based upon a human antibody. Results are compared to assays for Factor VIII coagulant activity (VIII:C) and Factor VIII related antigen (VIII:R:Ag) in plasma from 30 normal female individuals, 5 fetuses from mothers normal with respect to bleeding status, 10 obligate carriers of haemophilia A, 10 patients with haemophilia A, 5 with von Willebrand's disease, and 5 with haemophilia B. The ELISA developed is simpler than previously published VIII:CAG methods owing to its use of total IgG instead of immunologically affinity-purified antibodies. It is specific (as judged from clinical results), sensitive (detection limit: 0.005 units/ml), and sufficiently precise (between-assay coefficient of variation: 11%) for the purposes mentioned. The coefficient of correlation between VIII:CAG and VIII:C results is 0.86. The introduction of ELISA for quantitating VIII:CAG represents an advantage as compared to existing immunoradiometric assays (IRMA) mainly due to the stable and non-radioactive reagents used in the ELISA.

PMID: 6417826 [PubMed - indexed for MEDLINE]

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- ▶ The combined use of monoclonal antibody-based enzyme-linked immunosorbent assays (ELISA) for factor VIII antigen (VIII:Ag) and von Willebrand factor antigen (vWF:Ag) for the detection of carriers of haemophilia A. [Clin Lab Haematol. 1988]
- ▶ Enzyme linked immunosorbent assay (ELISA) for the measurement of factor VIII coagulant antigen (CAG) using haemophilic antibodies. [Br J Haematol. 1986]
- ▶ Simplified immunoradiometric assay for factor VIII coagulant antigen. [Thromb Haemostasis. 1982]
- ▶ Detection of the carrier state for classic hemophilia using an enzyme-linked immunosorbent assay (ELISA). [Blood. 1982]
- ▶ Measurement of factor VIII procoagulant antigen in normal subjects and in hemophilia A patients by an immunoradiometric assay and by an enzyme-linked immunosorbent assay. [Haemostasis. 1987]

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pic, as compared to photopic vision. It explains why blue colors appear relatively brighter in weak light and yellow hues appear relatively brighter in stronger light. Also *Purkinje phenomenon*, *Purkinje shift*. **quantal e.** An effect, such as death or the occurrence of a tumor, which either happens or does not happen, showing no gradation. Compare GRADED EFFECT. **relative biologic e.** RELATIVE BIOLOGIC EFFECTIVENESS. **second gas e.** An effect observed when a mixture of two anesthetic gases, such as nitrous oxide and oxygen, is breathed. The greater initial uptake from the alveoli of one of the gases (nitrous oxide) in pulmonary capillary blood will augment the inspiratory volume and increase the concentration and uptake of the second gas (oxygen). **side e.** SIDE-EFFECT. **Soret e.** The development of a concentration gradient in a tube of solution subjected to a prolonged temperature gradient. Also *Soret phenomenon*. **specific dynamic e.** SPECIFIC DYNAMIC ACTION. **Stiles-Crawford e.** The phenomenon in which light entering through the center of the pupil appears brighter than the same light when entering through a peripheral part of the pupil. **treppe e.** STAIRCASE PHENOMENON. **Tyndall e.** The rendering visible of a beam of light passing through a transparent medium containing suspended particles. Also *Tyndall phenomenon*. **variegated position e.** The emergence of a mutant phenotype in a diploid organism that is heterozygous for a mutant allele when the activity of the wild-type allele is partially or totally repressed by a change in the chromosome, such as heterochromatization, in the region of the genetic locus. **Venturi e.** The fall in pressure and increase in speed of flow observed when a fluid travels through a constricted portion of a tube. **Vulpian's e.** The slow contraction of the denervated lingual muscles which may be evoked by stimulating the chorda tympani after division of the hypoglossal nerve. **Wever-Bray e.** COCHLEAR MICROPHONIC POTENTIAL. **Zeeman e.** The separation of a spectral line into two or more lines, having different polarization properties, by placement of the source in a strong magnetic field. **effectiveness** \i'fekt'ivnis\ 1 The extent to which a drug or other agent achieves its intended therapeutic purpose. 2 The measure of the extent to which items of service, such as the number of treatments given, are successful in achieving defined goals of improving health or curing or controlling disease. **relative biologic e.** The ratio of the biologic effects produced by a given amount of ionizing radiation to those effects produced by an equal amount of radiation of a standard type, usually taken as 250 kV x rays. Also *relative biologic effect*. **effector** \i'fekt'ər\ An organ that responds to nervous impulses either by movement (muscle, chromatophore), secretion (exocrine and endocrine glands), or release of an electrical discharge (electric organ), as of an electric eel. Also *effector organ*. **allosteric e.** A substance that affects the activity of an enzyme by binding to it at a site other than the substrate-binding site. The rates at which metabolic conversion occur are often controlled in response to the needs of the organism by such effectors. **effemination** \i'fem'ənā'shən\ FEMINIZATION. **efferent** \ef'ərənt\ [L *efferens*, gen. *efferentis*, pres. part. of *efferre* (from *ex*- out, away + *ferre* to carry) to carry away] Conveying outward or away from the center, as nerve impulses, fluid such as blood or lymph, or information. Also *efferential*. Compare AFFERENT. **α-e.** A motoneuron or its myelinated axon of large caliber exclusively innervating extrafusal muscle fibers. It contributes to the early α-wave of an evoked ventral root neurogram. Also α-

fiber. **β-e.** A motoneuron or axon that supplies motor endplates to both extrafusal (skeletal) and intrafusal muscle fibers. Also *skeletofusimotor fiber*, *β-fiber*, *β motor fiber*. **dynamic γ-e.** A fusimotor neuron whose activation enhances the phasic response of the primary ending of a muscle spindle to an abrupt change, i.e., in spindle length. The effect is thought to be due to contraction of the nuclear bag, intrafusal fibers. **γ-e.** A small motoneuron or its myelinated axon that innervates one or more of the intrafusal fibers in a muscle spindle but none of the extrafusal fibers. Such small axons contribute to the relatively late wave in an evoked neurogram monitored from a ventral root. Most spindles receive two distinct types of γ-efferents, called dynamic and static γ-efferents. Also *γ-fiber*, *fusimotor fiber*. **general visceral e.** 1 Denoting the motor innervation of the heart, the smooth muscle, and glands of the viscera. 2 A general visceral efferent fiber. **somatic e.** 1 Denoting nerve fibers that transmit impulses to extra- and intrafusal fibers in muscle. 2 A somatic efferent fiber. **special visceral e.** 1 Denoting motor fibers innervating muscles of branchial-arch origin, i.e., the muscles of mastication, and those of the face, middle ear, pharynx, larynx, and upper esophagus. The sternocleidomastoid and trapezius muscles are usually included. 2 A special visceral efferent fiber. **static γ-e.** A fusimotor neuron whose activation depresses the dynamic sensitivity of the primary ending and enhances static discharge of the secondary ending in response to steady stretch. **visceral e.** 1 Denoting autonomic nerve fibers that innervate the internal organs. 2 A visceral efferent fiber. **efferential** \ef'ərən'shəl\ EFFERENT. **effervescent** [L *effervescentis*, gen. *effervescentis*, pres. part. of *effervesce* (from *ef-* out + *fervere* to begin to be hot or to boil, from *fervere* to burn, seethe, boil) to begin to boil] Rapidly producing gas in the form of small bubbles within a liquid. **efficacy** \ef'əkəsi\ The effectiveness of a therapy, drug, or other intervention in the theoretical optimal state under ideal conditions. **efficiency** [L *efficien(tia)* (from *efficiens*, pres. part. of *efficere* to effect) the power to effect] 1 The ratio of useful output of a dynamic system to the input, in terms of power, energy, quantity of electricity, etc. 2 In statistics, the degree of accuracy with which a sample statistic estimates the parameter of interest. **counting e.** INTRINSIC COUNTER EFFICIENCY. **detection e.** INTRINSIC COUNTER EFFICIENCY. **intrinsic counter e.** The ratio of the number of pulses actually counted to the number of particles reaching the detector in the same time. It is the product of the intrinsic detector efficiency and the window efficiency. Also *counting efficiency*, *detection efficiency*. **photopeak e.** PEAK-TO-TOTAL RATIO. **production e.** 1 The ratio of tissue formed to the energy intake by an organism. 2 Energy in the tissue formed divided by energy intake. **window e.** The ratio of the number of pulses passed by the electronic window of the pulse-height analyzer to the number delivered by the detector in the same time. It is not always identical to the peak-to-total ratio, since sometimes the window should not cover the whole total-absorption peak. **effloresce** [L *effloresce(re)* (from *ef-* for *ex-* out; out of + *florescere* to begin to blossom; from *flōs* a flower, blossom) to bloom, blossom] To lose water of crystallization or combined water when exposed to fairly dry air. The solid that effloresces thereby becomes covered with a powder of the dehydrated material. **efflorescence** \ef'flōres'əns\ [French; a flowering. See EFF-